cupying one of the segments of the great or small saphenous veins. The overlying skin is brownish red in colour, the subcutaneous tissue is indurated and in the centre can be felt a cord-like structure which is obviously a thrombosed vein. The areas are moderately tender. Careful search should be made for any evidence of arterial obliteration, as migrating phlebitis can be a precursor or concomitant finding in Buerger's disease. However, the majority of phlebitis migrans cases seen by the author have not shown early or subsequent criteria of Buerger's and have cleared following removal of some focus of infection, the most common of which is the tonsils.

Erythema induratum.—This condition occurs predominantly in females and is characterized by single, but more commonly multiple, painful areas involving the skin and subcutaneous tissue. The lower leg is more frequently involved than the thigh. The lesions are irregularly oval in shape, the skin is brownish red and firm and the underlying fatty tissue shows considerable induration. The areas are tender to palpation and, in their later stages, usually break down causing chronic ulceration. No gross venous or arterial abnormality is present in the limb. The condition is considered to be tuberculous in origin and the diagnosis is confirmed by biopsy, where the characteristics of a tuberculous granuloma are found. A careful search should be made for other evidence of tuberculosis elsewhere in the body.

Erythema nodosum.—This is an acute disorder associated with fever and general malaise occurring usually in younger people up to 30 years of age. It is characterized by nodules involving the skin and subcutaneous tissue varying in size from that of a pea to that of a fifty cent piece. These may occur on all extremities and also the trunk but are most common on the legs. They feel firm, are somewhat tender and vary from a pink to a purplish violet in colour. The main feature is that the original lesions subside and disappear in two to three weeks but others subsequently may occur in different locations. Ulceration in the involved areas does not occur and the entire illness is limited to six to eight weeks. Erythema nodosum is usually considered rheumatic in origin but may follow a severe case of one of the exanthemata especially in debilitated people.

SUMMARY

1. An attempt has been made to briefly outline the common causes for chronic leg disability as seen from the viewpoint of a peripheral vascular clinic.

2. The importance of a detailed history is emphasized, especially where a post phlebitis lesion is suspected. The methods of investigation are outlined.

3. Co-existing varicose veins frequently mask the true cause of the condition and the steps to arriving at a correct diagnosis are outlined.

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MEDICAL SHOCK AND DEATH FOLLOWING NEOARSPHENAMINE THERAPY FOR SYPHILIS

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WELL organized clinic and private practice routine in the management of syphilis rarely encounters immediate serious reaction from intravenous injections of arsenicals. However, when this reaction is fatal the magnitude of the tragedy and its rarity merit the report of such a case.

Stokes, Beerman and Ingraham[1] state:

"There is, however, much difficulty in distinguishing between avoidable and unavoidable morbidity and mortality. The administration of an arsenical to a patient with an obvious contra-indication may result promptly in death, not from the arsenical as such, but from its improper use. Such complications as pneumonia developing when drugs are given at the onset of an acute bronchitis; death from rupture of an aneurysm or from angina pectoris if treatment is begun without proper preparation; exfoliative dermatitis following a repetition of treatment in a patient who gives obvious warning signs that were overlooked; aplastic anæmia and fatal purpura developing under the same circumstances; death from a cerebral accident if an arsenical is given in a large dose to a patient with acute syphilitic involvement of brain (Herxheimer effect), cannot fairly be laid at the door of the drug. Such treatment reactions are not drug reactions in any proper sense, yet they are only too readily used by antagonists to discredit even the intelligent use of modern methods."

These authors state that: "the average risk of death (avoidable and unavoidable) ranges from between 1:7,000 and 1:11,000 injections

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in use of trivalent arsenicals. The unavoidable risk of death ranges between 1:56,000 and 1:162,000 injections. Good performance is estimated at 1:15,000 to 1:35,000 depending on material, system, dosage, etc."

CASE HISTORY

Mrs. F., a white woman aged 57, on June 14, 1947, while in police custody on the charge of "state of intoxication in a public place", was routinely examined by a venereal disease control worker, and showed a positive blood complement fixation test and 800 Kahn units.

Present illness.—On June 26, 1947, she reported to the Vancouver Clinic. A review of her previous record revealed that on June 9, 1931, she was diagnosed as primary syphilis, seropositive. Treatment consisted of 43 injections of novarsan from June 9, 1931 to June 30, 1933, and 9 injections of bismuth from April 12, 1932 to November 9, 1932. She tolerated arsenicals well. The blood Kahn remained positive, 4-plus, during the entire period of treatment and observation from August, 1931 to June, 1933. Complete investigation, commenced on June 26, 1947, showed a positive blood complement fixation and 2,000 Kahn units. A physical examination was entirely negative and a spinal fluid examination performed on July 2, 1947, showed a negative complement fixation 5 cells per c.mm., protein less than 15 mgm. per 100 c.c., and colloidal gold curve of 00000000. Our cardiologist after x-ray of chest, fluoroscopy, electrocardiogram and physical examination on July 9, 1947, found evidence of arteriosclerotic aortic and heart disease but no evidence of cardiovascular syphilis. The patient was diagnosed syphilis, acquired, late, latent, seropositive, and was placed on weekly bismuth subsalicylate 0.2 gm. intramuscularly for 10 weeks. On July 30, 1947, her quantitative blood Kahn showed 1,400 Kahn units, and the blood complement fixation was positive.

On September 10, 1947, neoarsphenamine was started cautiously. The normal dosage of neoarsphenamine is 0.3 to 0.45 gm., but due to the patient's age the dosage was reduced. She received neoarsphenamine 0.2 gm. on September 17. On questioning her on September 24, she said she was well and that she had tolerated past treatments well, so neoarsphenamine 0.3 gm. was administered. The patient showed no untoward symptoms while the injection was being given, 9.50 a.m. In about three minutes, however, she complained of some discomfort in the epigastric region and her face became very flushed. Her pulse became thready at 9.55 and 5 minims of adrenalin was administered by hypo. Five minutes later the consultant ordered adrenalin 4 minims to be repeated. Pulse was imperceptible, skin was cold and clammy. She complained of choking sensation (no vomiting) and abdominal pain. From 10.00 to 10.30 a.m. she had several involuntary stools. At 10.15 caffeine sodium benzoate was given by hypo and at 10.30 her pulse was still imperceptible, with apex rate of 150, so intravenous plasma 750 c.c. was commenced. At 12 noon the patient's condition had improved, but she remained quite cyanosed, so was transferred to the medical wards of the Vancouver General Hospital at 12.15 p.m. Examination showed cyanotic colour which was marked in the extremities. Radial pulse and blood pressure were not obtainable. Respirations were shallow and rapid. Apex rate was 120 per minute. Extremities were cold. The foot of the bed was elevated and oxygen administered by mask. Adrenalin minims 7 were given hypodermically and plasma, 400 c.c., intravenously. Her condition seemed to be improving, but pulse and blood pressure still were not obtainable. At 4.00 p.m. her face became ashen colour with deep cyanosis of extremities. She was semi-comatose with sighing respirations. Coramine ampoules ii intravenously and caffeine sodium benzoate ampoule i hypodermically were given. At 4.30, condition showing no improvement, adrenalin minims 7 hypodermically and B.A.L. 225 mgm. (2.2 c.c. 10% solution) were given intramuscularly. Oxygen was given continuously and plasma running slowly. At 6.15 p.m. in spite of further support with coramine and adrenalin, and artificial respiration, the patient died.

Post-mortem examination (17 hours after death, Dr. J. E. McDonagh).—The essential findings were as follows: There were numerous small subendocardial regions of ecchymosis. The myocardium and valves were not remarkable. The ascending thoracic aorta showed a moderate degree of atherosclerosis, scarring and linear fissures of the intima, suggestive of syphilitic aortitis, but there was no appreciable dilatation. The coronary arteries were widely patent throughout and revealed only minimal atherosclerosis.

The lungs showed marked generalized congestion and some œdema. The liver weighed 1,540 grams. The right lobe was deeply indented by scars which divided it into large irregular lobules, a typical picture of hepar lobatum. The parenchyma of these irregular lobules showed a normal architecture macroscopically. The left lobe was enlarged to about twice normal size.

The other organs including the brain showed nothing remarkable.

Histologic examination. — Sections from the myocardium of the left ventricle reveal small subendocardial hæmorrhages which extend a short distance into the muscle fibres. The appearances are not otherwise remarkable. Sections through the thoracic aorta show a picture of syphilitic aortitis, with lymphocytic and plasma cell infiltration in the adventitia, and vascularization and scarring of the media. Sections of the liver show large dense fibrous tissue trabeculæ containing many thin-walled blood vessels and a moderately heavy infiltration with lymphocytes and scanty plasma cells. The anatomic lobules are well preserved although showing a little periportal fibrosis and moderate dilatation of sinusoids. This is a picture consistent with hepar lobatum of tertiary syphilis. The spleen is congested with blood, this being particularly noticeable in the sinusoids. The Malpighian bodies are large and prominent. An especially striking feature is the very large germinal centre in many of these in which the cells are very loosely distributed, many having fragmented and pyknotic nuclei. There are fairly numerous macrophage cells present. These are the so-called "reaction centres" common in certain infections, intoxications and also described in anaphylactic reactions.

Sections of the mediastinal and retroperitoneal lymph nodes show well marked "reaction centres" similar to those seen in the spleen. There is also a moderate degree of hyperplasia of reticular endothelial cells of sinusoids. The kidney show only marked cloudy swelling of the proximal convoluted tubules.

The adrenals show marked fatty changes in the cells of the zona glomerulosa and somewhat less marked in the zona fasciculata and zona reticularis. One small lesion, just filling the high power field of the microscope, is found in the cortex and is probably a gummatous lesion. The centre is dense, amorphous, slightly eosinophilic material being traversed by several small strands of fibroblasts. This is surrounded by a zone of closely packed fibroblasts scantily infiltrated with lymphocytes. Sections of the brain show rather marked generalized vascular dilatation and minimal perivascular hæmorrhages in scattered places. There is marked siderosis of the larger blood vessels in the region of the basal ganglia. In some of these vessels there is very marked thickening of the intima which reduces the lumen to as much as one-half normal diameter.

In summary, the pathological findings are: syphilitic aortitis, syphilis of the liver (hepar lobatum), small gumma of adrenal gland, fatty degeneration of adrenal cortex, subendocardial petechial hæmorrhages, cerebral congestion, pulmonary congestion and œdema, "reaction centres" in lymph nodes and spleen, splenic congestion.

COMMENT

In individuals who have an almost immediately fatal outcome following trivalent arsenical, the following causes or explanations must be considered:

A. *Technical errors*: (1) *Acid arsphenamine.*—Little more need be said about this catastrophe as it is unpardonable, and the outcome is generally fatal in a patient who receives concentrated un-neutralized arsphenamine (606) in place of neoarsphenamine. (2) *Toxification of drugs.*—Possible cause of death in some instances, but it can generally be prevented by proper use of drugs as directed and proper storage, handling, etc. In clinical use this cause is often ruled out as other patients may have received treatment with trivalent arsenical from same container, and this was the case in this instance. (3) *Hurry and speed.*—The rates of injection must be as laid down by authorities on this subject. Some doubt does exist in certain schools that one can cause death by too rapid intravenous therapy with neoarsphenamine. However, alarming reactions can certainly result, especially the nitritoid reaction.

B. *Structural impairment.*—One must always consider a rupture of an aneurysm or the sudden occlusion of coronary vessels as cause of sudden death following neoarsphenamine injection in an individual with cardiovascular syphilis, when there has not been the usual precautionary preparation of the patient with a course of heavy metals, *e.g.*, bismuth. A Herxheimer reaction in a vital organ such as the heart may prove fatal.

C. *Idiosyncrasy.*—True idiosyncrasy is extremely rare and generally related to technical errors or unfamiliarity with the drug.

D. *Nitritoid crisis* has been advanced as a possible cause of sudden death and it may be well to review it briefly. It is pointed out that it is possible to produce a nitritoid reaction in any patient being treated with neoarsphenamine merely by increasing speed of injection. The symptoms are (Stokes, *et al.*[1]):

1. (*a*) Deep breath or two; (*b*) gulping two or three times in succession; (*c*) expression of anxiety or restlessness.
2. *2nd Stage*: (*a*) Suffusion of face—red blotching—late sign; (*b*) deep apoplectic flush and œdema of face and back with or without urticaria—flushing over body; (*c*) choking; (*d*) wheezing and stridor (asthma).
3. *3rd Stage*: (*a*) Unconsciousness—pupils dilated—eyes open; (*b*) pulselessness and collapse (rare); (*c*) slow recovery is rule.

However, Stokes, *et al.*[1] state: "we have never, however, seen or encountered a record of death from true nitritoid crisis". Moore[2] likewise states: "instances of death during nitritoid reaction have been reported but we have never seen one".

E. *Colloidoclastic shock* is some times advanced as a cause of sudden death and is described by Stokes, *et al.*[1] as follows:

> "Colloidoclastic shock associated with acid arsphenamine administration and so-called arsphenamine collapse differs sharply from nitritoid collapse as it develops, in that in shock the patient is pale, pulseless and collapsed as compared to nitritoid where he is flushed, hyperactive, coughing, choking, with a bounding pulse that may momentarily collapse." Moore,[2] however, makes no mention of this phenomenon.

F. *Shocklike reactions (medical shock).*—This is described by Moore[2] as a condition clinically similar to acute surgical shock, seen rarely in patients in whom intravenous injections of an arsphenamine have been given. This reaction has not been noted following use of mapharsen. In a report of three cases of medical shock following intravenous therapy with neoarsphenamine Weinberg[3] states the type of shock produced by neoarsphenamine is:

> "Characterized by weakness, grayish cyanosis, cold clammy skin, nausea and vomiting, collapse and syncope; the pulse is weak, rapid and thready or even impalpable; the blood pressure is lowered to alarming levels or even . . . unobtainable. There is rapid dehydration, diminished blood volume, increased blood nitrogen and some times anæmia. It is not relieved by use of adrenalin in contrast to nitritoid crisis."

None of the above three cases had a fatal outcome, although heroic efforts were necessary to prevent death. It is noted, however, that in all three cases the reaction occurred following the second or third intravenous injection in a neoarsphenamine series.

One case has been reported by Orr[4] as medical shock following neoarsphenamine. The term medical shock was first used by Atchley[5] to describe a state of vasomotor collapse not due to trauma. The features of medical shock produced by neoarsphenamine are very similar to those seen in more frequently encountered surgical shock. Both show a drop in blood pressure and increased hæmoglobin and erythrocyte count in peripheral blood. There is generally a dilatation of capillaries with resultant stasis of blood and lack of oxygen to surrounding tissues and a resultant disproportion between blood volume and vascular bed. Phelps[6] and Helfors[7] have each reported cases which had a fatal outcome

following intravenous neoarsphenamine. Both these could possibly be placed in the category of medical shock. It is at least suggested by experimental work of Hirano[8] on adrenal glands in animals poisoned with arsphenamine that this reaction may be due to acute adrenal injury.

G. *Arsphenamine reactions due to myocardial injury.*—Moore[2] states that when large doses of an arsphenamine are given to a patient with cardiovascular syphilis, there may occur an immediate, very severe and often fatal reaction. This appears during the injection or within a very few minutes thereafter. It is characterized by fainting, ashy gray-green pallor, and profuse sweating; the pulse becomes rapidly imperceptible, the patient gives a few gasps and dies. Before the danger of intensive treatment of cardiovascular syphilis was appreciated, at least four deaths occurred in Moore's clinic. The electrocardiographic studies of Reid[9] and Wilson[10] and his collaborators have indicated that this type of reaction is probably due to the sudden production of ventricular fibrillation in an already damaged myocardium. Curiously enough, this difficulty is apparently confined almost exclusively to patients with pre-existing myocardial damage due to cardiovascular syphilis. It has not been observed in individuals with rheumatic, hypertensive or arteriosclerotic heart disease. This type of reaction has not been reported following mapharsen.

Stokes, *et al.*[1] described cardiovascular collapse which is characterized by greenish pallor or cyanosis with dizziness, sweating, low pulse, and feeble heart sounds in marked collapse. They further state that cardiac death after arsenicals without any technical fault or idiosyncrasy can nearly always be traced to pre-existing cardiac disease, usually syphilitic in character and involving coronary vessels, or may be associated with the effect of the therapeutic shock (Herxheimer) or aneurysm with resultant rupture and death. They emphasize that any history of alcoholism predisposes to reactions following intravenous neoarsphenamine.

In the case which we have described it was not until the third injection of neoarsphenamine that any reaction occurred, so we can assume that she did not have a Jarisch-Herxheimer reaction involving a vital organ, such as heart or brain, and which one would have expected after the first rather than third arsenical injection. Further, the post-mortem findings also ruled this out as a possibility. It is interesting to note that a careful physical, fluoroscopic, electrocardiographic and roentgenographic examination failed to reveal any cardiovascular syphilis yet there was evidence of subclinical syphilitic aortitis at autopsy. The dramatic onset and the clinical picture of profound cardiovascular collapse with but temporary response to the heroic measures used to combat shock would indicate that this case could very well be ascribed to the rare cause of death following neoarsphenamine previously mentioned, namely, medical shock. The fact that the patient was an alcoholic is undoubtedly a contributory factor to this fatal reaction.

This type of reaction impresses us with the urgent character of treatment called for and the need and availability of adequate hospital care, as it is an emergency of utmost importance. Orr[11] feels that in cases where there is an element of doubt as to the diagnosis between medical shock and nitritoid crisis, failure to respond within two or three minutes to a single injection of adrenalin should support a diagnosis of medical shock. He further believes that cases of medical shock can be controlled at once by the introduction into the blood stream of a quantity of normal saline solution sufficient to fill the greatly increased area of the capillary vascular bed. The amount required may be very great. In his own case two litres were necessary to restore the systolic pressure to 60 mm. of mercury and Orr[12] mentions a case reported by Atchley (in which the shock was caused by a rattlesnake bite) where 7,200 c.c. of saline were given in the course of 16 hours. He recommends[11] that flasks containing normal saline with sterile sets ready for intravenous use should be available at all times at clinics for such emergency. We can but conjecture as to the results of earlier administration of B.A.L. This case received an injection of B.A.L. six and a half hours after onset of symptoms.

We hope that the time is not too distant when such tragedies will be averted. This hope is strengthened by the reports of low toxicity and minor reactions to the latest drug used in the treatment of syphilis, namely penicillin. As a direct result of the above case in the Division of V.D. Control, Department of Health and Welfare, Province of British Columbia, we have decided that all cases of known alcoholics with

syphilis shall be treated with either penicillin alone or penicillin and bismuth.

CONCLUSIONS

1. A middle-aged white female confirmed alcoholic, developed medical shock with a fatal outcome following neoarsphenamine therapy in the treatment of her syphilis.

2. Suggestions and recommendations are made as to the diagnosis and management of medical shock following neoarsphenamine therapy.

3. It is recommended that syphilis in a confirmed alcoholic be treated with penicillin alone or with penicillin and bismuth, but not with an arsenical.

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VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM*

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VIRUS infections of the central nervous system present a major problem in many parts of the world and specially in North America. The most frequently diagnosed nervous diseases of virus etiology in this continent are poliomyelitis, equine encephalomyelitis, St. Louis encephalitis, lymphocytic choriomeningitis, rabies, and meningitis associated with mumps or herpes. With present facilities for rapid air travel it is quite possible, however, for cases of nervous disease contracted in any part of the world to be seen by physicians in Canada and America. Unless such physicians are well acquainted with the whole range of neurotropic virus diseases, mistaken diagnoses may be made, and valuable specimens for laboratory tests may not be collected. Furthermore, such cases may come to be reported in the literature as suffering from "a hitherto undescribed infection", when in reality they are suffering from a disease well-recognized elsewhere.

My object in this paper is to mention briefly the recognized virus infections of the central nervous system that have been described in all parts of the globe; this will be done by discussing a simple scheme into which these infections can be classified. Laboratory tests are available for the diagnosis of many of these diseases; the present scope of these investigations has recently been outlined elsewhere (Rhodes, 1948).

At least 35 antigenically distinct strains of viruses can cause an infection of the central nervous system in man. Many of these viruses differ widely one from another in biological properties, but others are closely related. Of recent years, a number of studies have been carried out on the antigenic relationships of neurotropic viruses, and this information enables us to build up a reasonable classification. The methods used in these studies include complement fixation and virus neutralization tests, and cross resistance tests in immunized laboratory animals. However, a classification based on antigenic structure is of little value to the clinician, who requires something more practical, something that will help particularly in the differential diagnosis of an obscure case of nervous disorder of presumed viral origin. Accordingly, I have fitted the various infections of the central nervous system into a mainly clinical, pathological, and epidemiological framework, but it should be borne in mind that the primary basis of subdivision is antigenic structure.

The first and most obvious differentiation is between (*a*) those viruses in which nervous involvement is only secondary to a primary localization of the virus elsewhere in the body; and (*b*) infections due to the neurotropic viruses proper, where the primary localization of the virus is in the central nervous system. We shall concern ourselves, in this paper, chiefly with the neurotropes proper.

* Portion of an address given to the Montreal Neurological Society, January 28, 1948.